Abstract
In the field of oral delivery, pulsatile-release dosage forms are drawing increasing interest. After administration, these systems are able to elicit programmable lag phases followed by a prompt or rate-controlled liberation of drugs. Such a release mode has been described as potentially suitable for accomplishing chronotherapeutic goals, particularly in the case of widespread chronic pathologies with prevailing night or early-morning symptoms, such as bronchial asthma and cardiovascular disease. Moreover, time-dependent colon delivery can also be achieved when pulsatile delivery systems are conveniently adapted to overcome the variability in gastric emptying time and yield lag phases approximately corresponding to the small intestinal transit time. Delayed liberation of drugs has been attained through a range of formulation approaches, namely reservoir, capsular and osmotic release platforms. Based on the above-mentioned premises, the aim of this article is to outline the rationale behind oral pulsatile delivery and the main relevant design strategies.

Keywords
Oral delivery, pulsatile release, delayed release, chronotherapy, lag time, swellable hydrophilic polymers

Recently, it has been highlighted that the time at which a medication is administered may play a pivotal role in determining the outcome and tolerability of a pharmacological therapy. The temporal rhythms of bodily functions have indeed been demonstrated to affect not only the incidence and severity of a vast array of chronic pathologies, but also the pharmacokinetics as well as the pharmacodynamics of most bioactive compounds in use.1,2 As a result, chronotherapeutic treatments tailored to provide the patient with the appropriate dose of the required drug in a timely manner are of high current interest.

In the field of drug delivery, pulsatile release is recognised as a suitable strategy for meeting the aforementioned chronopharmaceutical needs in that it involves the programmable liberation of drugs following lag phases that commence upon administration.3 The release process may be started in response to external stimuli (e.g., chemical, thermal, electric and magnetic signals) or, alternatively, may depend on inherent mechanisms only. This is the case with time-controlled devices, which are expected to perform consistently regardless of major physiological variables, such as pH, ionic strength and temperature. Because of constraints related to the gastrointestinal transit time, circadian or ultradian variation patterns in disease manifestations and/or drug fate are the only viable targets for pulsatile delivery systems intended for the oral route. In particular, their performance would apply to the management of pathologies with prevailing night or early-morning recurrence, such as cardiovascular disease, bronchial asthma, rheumatoid arthritis and sleep disorders. Administered at bedtime, pulsatile release medications could in these instances elicit pharmacological protection when mostly required either entailing without an unnecessary sustained drug exposure in the patient on the one hand, or the interruption of normal sleep patterns on the other, which would reflect negatively on the overall treatment compliance.

When yielding repeated release profiles, oral pulsatile delivery systems can also be employed to accomplish multiple daily dosing regimens for drugs that fail to be eligible for prolonged-release formulations, e.g. in the case of a strong first-pass effect or development of pharmacological tolerance. Furthermore, pulsatile release is exploited to target proximal and distal colonic regions via the oral route based on a time-dependent design strategy.4,5 For this purpose, in vivo lag periods are sought that would roughly correspond to the relatively reproducible small intestinal transit time of dosage forms. In addition, the application of outer enteric-soluble films is generally required in order to overcome unpredictable gastric emptying. Colon delivery is drawing increasing research interest because of its proven advantageousness in the treatment of inflammatory bowel disease (IBD) and potential role in the chemoprevention of colorectal adenocarcinoma.6 Moreover, despite its modest absorptive characteristics, the large bowel is recognised as a gateway to the systemic circulation. In this respect, colonic release is under extensive investigation to enhance the oral bioavailability of peptides, proteins, oligonucleotides and nucleic acids, which mostly exhibit poor gastrointestinal stability and permeability characteristics.7 Indeed, recent advances in biotechnology have made a large number of such drugs available on a production scale, thus strengthening the need for non-parenteral delivery modes with a higher rate of patient...
Delivery

136

compliance. For pulsatile release purposes, a variety of formulation strategies have been proposed, including reservoir, capsular and osmotic formulations.\(^{16,17}\)

**Reservoir Systems with Release-controlling Coatings**

Reservoir systems, which encompass a wide range of delivery platforms, are presented in the form of single- or multiple-unit formulations. The latter offer well-defined advantages, particularly in terms of performance consistency because of a lower impact of gastric residence variability. In both cases, they comprise an inner drug core and a release-controlling coat layer. Based on the delivery mechanism involved, which in turn depends on the physical-chemical characteristics of the coating material, erodible, rupturable and diffusible systems have been identified. Erodible reservoir devices are provided with swellable hydrophilic polymeric barriers.\(^{18}\) When in contact with the aqueous media, these are typically subject to swelling, dissolution and/or erosion phenomena, thus delaying the onset of drug release for a time interval that can be programmed by selecting the appropriate polymer and coating level. Such layers are mostly based on hydrophilic cellulose derivatives, such as hydroxypropyl methylcellulose (HPMC), hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC), that ensure established safety and versatility profiles.

An early example of a pulsatile delivery system based on hydrophilic cellulose ethers was a three-layer tablet in which two different drug compartments were separated by an intermediate HPMC barrier.\(^{19}\) The device was coated with an impermeable film except for the surface of one drug-containing layer, which was allowed to interact with the aqueous medium, thus providing an immediate release pulse. A second pulse occurred after extensive erosion of the intermediate barrier. Lag time was proved to depend on the viscosity of the polymeric mixture the barrier was composed of. Reproducible double-peak plasma concentration curves of a model drug were attained in agreement with the observed in vitro performance. As a subsequent development of this device, the Chronotopic™ system was proposed.\(^{20}\) It consists of a single- or multiple-unit drug core completely surrounded by an HPMC coating. Particularly in the early stages of development, the application of the functional layer turned out to be a challenging step. Initially, press-coating and hydro-organic spray coating were attempted.\(^{21}\) However, both techniques were abandoned because of a number of major drawbacks. Indeed, press-coating involved remarkable versatility constraints, whereas the use of organic solvents was related to well-known environmental and safety issues. Aqueous spray coating was therefore investigated with differing HPMC grades.\(^{22}\) A low-viscosity polymer (Methocel®ES50) was shown to offer an acceptable balance of various important aspects, such as process feasibility, effectiveness in delaying drug liberation, flexibility in lag time modulation and limited impact on release rate. Programmable and reproducible lag phases followed by a fast drug liberation were achieved both in vitro and in healthy volunteers. These results were supported by \(\gamma\)-scintigraphic data, which also demonstrated the ability of the device to accomplish time-based colon delivery when provided with an outermost gastric-resistant film.\(^{23}\) The above-mentioned aqueous spray coating procedure was successfully applied to gelatin capsules, selected as alternative cores because of their suitability for conveying multiparticulate formulations (micro- and nanoparticles) potentially beneficial to the intestinal absorption of protein drugs.\(^{24}\)

In addition, systems based on bovine insulin-containing core tablets were prepared, with or without enzyme inhibitor and absorption enhancer compounds.\(^{25,26}\) Also in this case, satisfactory stability and in vitro release characteristics were obtained. Furthermore, the use of innovative coating techniques, such as tangential spray coating in rotary fluid bed and powder layering, was explored with the aim of improving the yield and reducing the time of the manufacturing process, thus further enhancing its potential for scalability.

Combinations of high- and low-viscosity HPMC grades were employed for the preparation of a press-coated erodible system.\(^{27}\) When increasing the low- versus high-viscosity HPMC ratio, shorter lag phases and a faster absorption were observed. Moreover, double-peak concentration curves were achieved when splitting the drug dose between the core and coating formulations. In a different instance, a low-viscosity HPMC press-coated tablet (PCT) was provided with a buoyant high-viscosity HPMC layer containing sodium bicarbonate, thus resulting in a floating pulsatile release platform.\(^{28}\) When HEC and HPC were employed as press-coating agents, in vitro and in vivo lag times were analogously proved to lengthen as a function of the amount and viscosity grade of the employed cellulose derivative.\(^{29,30}\) HPC was recently subjected to injection moulding processes for the manufacturing of novel swellable/erodible shell devices (ChronoCap) able to convey differing formulations and release a variety of bioactive compounds after the needed lag phases.\(^{31}\) The peculiar advantages offered by this technology would thus reside in the high versatility and the possibility of dealing with the core and the release-controlling barrier as independent formulation items, thus ideally limiting the technical and regulatory burden connected with pharmaceutical development.

To prepare press-coated systems, water-swellable materials other than cellulose ethers were also exploited. Erodible coatings based on spray-dried composite lactose powders containing sodium alginate–chitosan complexes were shown to withstand acidic media and delay, through their hydration and erosion processes, the release of drugs in pH 6.8 fluids.\(^{32}\) Lag time was affected by the coating level and deacetylation degree of chitosan. Tablets loaded with a highly soluble excipient and dry coated with polyethylene oxide (PEO) blends were designed to face the decrease in bioavailability possibly connected with delivery into distal intestine regions where water content is limited.\(^{33}\) PEO was used for the preparation of the swellable layer that was applied by double compression onto the free surface of a core tablet surrounded by an impermeable shell.\(^{34}\) When PEO was replaced with sodium alginate or sodium carboxymethylcellulose, shorter and longer delay phases were observed, respectively, in agreement with the swelling characteristics of the investigated materials. The SyncroDose™ delivery technology was developed including a drug-containing tablet and an erodible dry-coating layer composed of xanthan and locust bean gum.\(^{35}\) The lag phase could be modulated by varying the ratio between these polysaccharides.

In an attempt to overcome the drawbacks related to conventional press-coating, alternative technologies were set up such as the one-step dry-coated tablet (OSDRC) and PCT, which were based on HPMC and low-substituted HPC (L-HPC)/glyceryl behenate as erodible barrier components, respectively.\(^{36,37}\) When administered to beagle dogs, PCT prototypes were proven to elicit reproducible in vivo lag times increasing as a function of the per cent amount of glyceryl behenate in the coating.\(^{38}\) The erodible layer of the Time-Clock®
system was prepared differently, with hydrophobic blends of natural waxes and surfactants applied onto tablet cores by spray coating of water dispersions at rather elevated temperatures. In this case, the delay preceding drug release was accounted for by the re-dispersion of the hydrophobic coating materials into the aqueous fluids. In vivo pharmacokinetic and γ-scintigraphic investigations pointed out reproducible lag times regardless of food intake.

As far as rupturable reservoir systems are concerned, the time-programmed liberation of bioactive compounds is enabled by the disruption of a moderately water-permeable outer membrane based on insoluble polymeric materials often in admixture with plasticising and pore-forming excipients. The disruption step is induced by an increase in the volume of the core formulation that may in turn result from an osmotically driven water influx or hydration of highly swellable polymers. The release onset is mainly controlled by the thickness and composition of the rupturable coating.

In the pulsatile release tablet (PRT), for example, the disruption of a press-coated layer composed of co-melted hydrogenated castor oil and polyethylene glycol (PEG) 6000 was brought about by the swelling of sodium carboxymethylcellulose, a superdisintegrant contained in the core.32 The delay phase was modulated by varying the thickness and PEG content of the coating. The same swellable agent was selected for application onto tablets or gelatin capsules to form an expansion layer interposed between the drug-containing core and an ethylcellulose (EC) outer film. Typical pulsatile release patterns were achieved using these systems. Their lag time was generally prolonged by raising the coating level and/or decreasing the amount of channelling agent (HPMC) in the EC membrane. Polyvinyl alcohol (PVA) was incorporated in the tablet core of the swelling controlled release system (SCRS) to provide the swelling pressure needed to rupture the EC film. The amount of HPMC in the release-controlling coat and the PVA content of the core were proved to be the chief determinants of the lag phase duration. Moreover, EC mixtures with the enteric-soluble methacrylic acid copolymer Eudragit® L were employed to film-coat a core tablet including the swelling agent crospovidone in its composition. In a different instance, the hydrostatic pressure responsible for breaking up the EC membrane was developed by carbon dioxide generated inside the core following dissolution of charged quaternary ammonium groups and the hydrophobic segments of the acrylic polymer, thus giving rise to a rapid increase in the permeability of the outer coating.

Capsular Systems with Release-controlling Plugs

The pulsatile delivery of drugs from capsular systems is based on the time-programmed ejection of a plug matrix from an insoluble capsule body filled with the drug formulation. The time to ejection coincides with the lag phase, which depends on the physical-chemical properties, size and position of the plug. This was composed of cross-linked PEG 8000 hydrogel in the original Pulsicap device, the suitability of which for time-controlled release was extensively assessed by human imaging investigations. In order to overcome the possible constraints associated with the use of a non-approved cross-linked, swellable material, erodible hydrophilic polymers such as HPMC, PVA and PEO were later employed to prepare the matrix plug. In the Programmable Oral Release Technologies (PORT™) device, an insoluble plug was alternatively used to seal the opening of a semi-permeable capsule body that contained osmotically active agents along with the drug molecule. A capsule-like design was exhibited by the Egalet® delivery platform. When intended for pulsatile release, such a system comprised a cylindrical impermeable shell containing a drug core and two injection-moulded erodible plugs (high-molecular-weight PEG or PEO/PEG monostearate) at each end. By varying the size and composition of the plug and drug formulations, it was possible to define onset and rate of delivery.

Osmotic Systems

The osmotic pump mechanism was exploited in order to develop a once-a-day controlled-onset extended-release (COER-24) formulation of verapamil hydrochloride aimed at the chronotherapy of cardiovascular disease. According to the OROS® Push-Pull™ technology, COER-24 was composed of a core tablet, entirely coated by a semi-permeable film, including a polymeric push compartment and a drug compartment. The latter was connected with the outer environment via two laser-drilled micropores. An additional hydrophilic coat was interposed between the core and the semi-permeable membrane to further prolong the delay preceding the release onset. Upon water influx, the active ingredient was solubilised and the push compartment started swelling. As a result, the drug solution was pumped out at a constant rate through
the micropores drilled into the external coating. The release of verapamil was demonstrated to occur over a period of several hours after a four- to five-hour lag time. A good in vitro–in vivo correlation was assessed, thus highlighting the suitability of COER-24 for meeting the well-established chronotherapeutic requirements of cardiovascular disease.

Conclusion

The variety of formulation approaches and large number of delivery systems presented highlight the current interest in the field of oral pulsatile delivery: indeed, the identification of temporal variation patterns for more pathological conditions and the consolidation of chronotherapeutic principles, coupled with an increasingly attentively considerate for patient compliance, are likely to further enhance research efforts in this particular area of pharmaceutics. Innovation, scalability, lack of severe regulatory constraints and availability of human proof-of-concept results will most likely represent the key issues in the successful development of any delivery technology proposed.

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